a2 cont'd 43. The method according to claim 35 wherein the animal has a neoplastic disease.

Remarks

Support for the amendments to claims 29, 32, and 35 may be found, for example, on page 16, lines 23 through 25 and page 2, line 26 through page 5, line 29.

Support for the amendments to claims 30, 33, and 36 may be found, for example, on page 15, lines 12 through 17; on page 16, lines 4 through 11; on page 16, line 31 through page 17, line 6; and on page 2, line 26 through page 5, line 29.

Support for the amendments to claims 31, 34, and 37 may be found, for example, on page 15, lines 12 through 17; on page 16, lines 4 through line 9, and lines 13 through 16; on page 16, line 31 through page 17, line 1, and lines 6 through line 10; and on page 2, line 26 through page 5, line 29.

Basis for added claims 38 – 43 may be found, for example on page 16, lines 4 through 9, and line 13.

No new matter has been added.

Interview

Applicants thank Examiner Huang for the personal interview on November 13, 2002 with the undersigned and Dr. Ann Mueting, counsel for Applicants. During the interview the claim rejections were discussed, as were the accompanying amendments and arguments.

35 U.S.C. § 112, First Paragraph, Rejection

Claims 29-37 are rejected under 35 U.S.C. 112, first paragraph, on the grounds that the specification, while being enabling for the use of the inventive compounds for inducing biosynthesis of interferon alpha or tumor necrosis factor, allegedly does not reasonably provide enablement for the use of the compounds for inducing cytokine biosynthesis and for treating any viral diseases and neoplastic diseases, and does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

This rejection is traversed. Reconsideration of and removal of this rejection is respectfully

requested.

Regarding claims 29, 32 and 35, directed to a method of inducing cytokine biosynthesis in an animal, the specification provides sufficient information to enable those skilled in the art to use the inventive compounds not only for biosynthesis of IFN-α or TNF-α, but also for IL-1, 6, 10, and 12, and a variety of other cytokines. (See, for example, page 15, lines 14 through 16.) Further guidance on how to accomplish this is provided, for example, on page 16, lines 23 through 31, and on page 14, lines 28 through page 15, line 6.

In addition, those skilled in the art of cytokine biosynthesis have known that IFN-α directly or indirectly up-regulates the activity of other cytokines, for example, IFN-γ, IL-1, IL-1R, IL-2, Il-2R, IL-6, IL-8, IL-12, IL-15, IL-18R, and ISG-15. This is discussed on pages 566, second column, and 567, first column of a recent review (Brassard et al., *J. Leukocyte Biology*, 71, 565-581 (2002)), **Exhibit A**, which provides eight references dated 1993-1999 from which these and other examples were taken.

Applicants have provided a large number (221) of Examples that show IFN-α induction. These Examples include a wide variety of R_1 groups, many of which are unsubstituted and substituted cycloalkyl, aryl, heteroaryl, and heterocyclyl. (Examples of such aryl include Examples 20, 28, 29, 31, 32, 38, 50, 58, 67, 68, 113, 158, 205, 210, 211, 224, 226, 231; substituted aryl include Examples 1, 7, 9, 11, 21-27, 30, 33, 37, 40-43, 45-48, 52, 59, 61, 64, 65, 69, 78-81, 83-88, 90-93, 95-98, 100, 102-107, 110, 114, 120-122, 127, 128, 138, 152, 154, 159-161, 184, 206, 213 (Examples 11, 30, 43, and 69 being aryl substituted with heteroaryl, 41 and 96 being aryl substituted with aryl, 102 being aryl substituted with heterocyclyl); heteroaryl include Examples 3, 19, 44, 57, 109, 112, 204; substituted heteroaryl include Examples 77, 94, 99, 101, 123, 131, 215; heterocyclyl include Example 229, substituted heterocyclyl include Example 227; and substituted cycloalkyl include Examples 73, 89, 148, 200, 212.) Given the level of skill in the art, sufficient direction and guidance has been provided in the specification for one skilled in the art to practice the full scope of the claimed method of inducing cytokine biosynthesis. The compound claims were issued in 6,331,539.

Claims 30, 33 and 36, directed to a method of treating a viral disease in an animal, have been amended to specify a compound of the formula (I) that induces cytokine biosynthesis and to specify an animal in need thereof. The specification provides sufficient information to enable those

skilled in the art to use the inventive compounds not only for induction of cytokine biosynthesis, but also for treatment of viral diseases. (See, for example, page 15, lines 12 through 17 and page 16, lines 4 through 11.) Further guidance on how to accomplish this is provided, for example, on page 16, line 31 through page 17, line 6, and on page 14, line 28 through page 15, line 6. Furthermore, the abstract of Brassard et al., *J. Leukocyte Biology*, 71, 565-581 (2002), **Exhibit A**, states the following: "Interferon-α (IFN-α) has proven to be a clinically effective antiviral and antineoplastic therapeutic drug for more than 16 years. During this time, evidence from in vitro laboratory studies and the clinical arena has supported the concept that IFN-α is an immunotherapeutic drug. By regulating a diverse set of cytokines and their receptors, IFN-α is uniquely positioned to prime the host immune response and provide an effective antineoplastic- and antiviral-immune response."

Applicants have provided a large number (221) of Examples that show IFN-α induction. These Examples include a wide variety of R_1 groups, many of which are unsubstituted and substituted cycloalkyl, aryl, heteroaryl, and heterocyclyl as shown above. Given the level of skill in the art and in view of the discussion above, sufficient direction and guidance has been provided in the specification for one skilled in the art to practice the full scope of the methods as claimed for treating viral diseases using the compounds of the present invention.

Claims 31, 34 and 37, directed to a method of treating a neoplastic disease in an animal, have been amended to specify a compound of formula (I) that induces cytokine biosynthesis, limit the neoplastic disease being treated to melanoma, hairy cell leukemia, and myelogenous leukemia, and specify an animal in need thereof. The specification provides sufficient information to enable those skilled in the art to use the inventive compounds not only for induction of cytokine biosynthesis, but also for treatment of neoplastic diseases. (See, for example, page 15, lines 12 through 17 and page 16, lines 4 through 16.) Further guidance on how to accomplish this is provided, for example, on page 16, line 31 through page 17, line 10, and on page 14, line 28 through page 15, line 6. Furthermore, the abstract of Brassard et al., *J. Leukocyte Biology*, 71, 565-581 (2002), **Exhibit A**, states the following: "Interferon-α (IFN-α) has proven to be a clinically effective antiviral and antineoplastic therapeutic drug for more than 16 years. During this time, evidence from in vitro laboratory studies and the clinical arena has supported the concept that IFN-α is an immunotherapeutic drug. By regulating a diverse set of cytokines and their receptors, IFN-α

is uniquely positioned to prime the host immune response and provide an effective antineoplastic- and antiviral-immune response." This review reference (Exhibit A) also points out that IFN-α has been used with success to treat melanoma patients and refers to a 1998 reference. This is shown at page 572, first column, under **Melanoma** in Exhibit A. The review reference (Exhibit A) points out that Hairy Cell Leukemia is an FDA-approved clinical indication for IFN-α and refers to a 1998 reference. This is shown on page 569, second column, under **IFN-α As An Immunotherapeutic Protein** in Exhibit A. The review reference (Exhibit A) points out that "IFN-α uses immunological mechanisms to down-regulate CML (chronic myelogenous leukemia) cell growth" and that "prolonged patient survival times are observed with IFN-α treatment", referring to a 1998 reference. This is shown on page 572 at the top of the first column of Exhibit A.

Applicants have provided a large number (221) of Examples that show IFN-α induction. These Examples include a wide variety of R_1 groups, many of which are unsubstituted and substituted cycloalkyl, aryl, heteroaryl, and heterocyclyl as shown above. Given the level of skill in the art and in view of the discussion above, sufficient direction and guidance has been provided in the specification for one skilled in the art to practice the full scope of the methods as claimed for treating the neoplastic diseases, melanoma, hairy cell leukemia, and myelogenous leukemia, using the compounds of the present invention.

Accordingly, applicants respectfully request that the 35 U.S.C. § 112 rejection be withdrawn.

Statutory Type (35 U.S.C. § 101) Double Patenting Rejection

Claims 1-28 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-28 of prior U.S. Pat. No. 6,331,539. Since claims 1-28 are now cancelled, this rejection is overcome and withdrawal of the rejection is respectfully requested.

Obviousness-Type Double Patenting

During the interview, the Examiner stated that claims 29-37 are also subject to rejection under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 29-31 of U.S. Patent No. 6,331,539. Included herewith is a terminal disclaimer in compliance with 37 CFR 1.321(c) and 37 CFR 3.73(b). Accordingly, Applicants respectfully

request that the obviousness-type double patenting rejection be withdrawn.

Conclusion

The above amendments and remarks address each of the issues raised by the Examiner in the outstanding office action. Examination and reconsideration of the claims and early favorable action are respectfully requested. The Examiner is invited to contact the undersigned if the Examiner believes any remaining questions or issues could be resolved by doing so.

Respectfully submitted,

Registration Number	Telephone Number
46,689	651-733-7830
Date	
November 19, 2002	

By _____
Dean A. Ersfeld

Office of Intellectual Property Counsel
3M Innovative Properties Company
P.O. Box 33427
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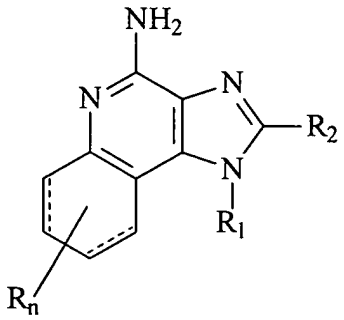
Version With Markings to Show Changes Made

29. A method of inducing cytokine biosynthesis in an animal comprising administering and effective amount of a compound of [claim 1]the formula (I):



(I)

wherein

R_1 is -alkyl-NR_3- SO_2 -X-R_4 or -alkenyl-NR_3- SO_2 –X-R_4 ;

X is a bond or –NR_5-;

R_4 is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

-O-$(alkyl)_{0-1}$-aryl;

-O-(alkyl)$_{0-1}$-substituted aryl;

-O-(alkyl)$_{0-1}$-heteroaryl;

-O-(alkyl)$_{0-1}$-substituted heteroaryl;

-O-(alkyl)$_{0-1}$-heterocyclyl;

-O-(alkyl)$_{0-1}$-substituted heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-S(O)$_{0-2}$ -alkyl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-aryl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-substituted aryl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-heteroaryl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-substituted heteroaryl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-heterocyclyl;

-S(O)$_{0-2}$ –(alkyl)$_{0-1}$-substituted heterocyclyl;

-(alkyl)$_{0-1}$-NR_3R_3;

-(alkyl)$_{0-1}$-NR_3-CO-O-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-aryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted aryl;

-(alkyl)$_{0-1}$-NR_3-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted heteroaryl;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkyl;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and in the case of alkyl, alkenyl, or heterocyclyl, oxo;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

- alkyl-O-alkyl;

- alkyl-O- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

$-N(R_3)_2$;

$-CO-N(R_3)_2$;

$-CO-C_{1-10}$ alkyl;

$-CO-O-_{C1-10}$ alkyl;

$-N_3$;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

-substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);

-CO-heteroaryl; and

-CO-(substituted heteroaryl);

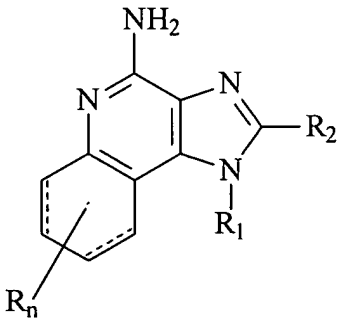
each R_3 is independently selected from the group consisting of hydrogen and C_{1-10} alkyl;

R_5 is selected from the group consisting of hydrogen and C_{1-10} alkyl, or R_4 and R_5 can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

n is 0 to 4 and each **R** present is independently selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen and trifluoromethyl,

or a pharmaceutically acceptable salt thereof, to the animal.

30. A method of treating a viral disease in an animal in need thereof comprising administering to the animal an effective amount of a compound of [claim 1]the formula (I) that induces cytokine biosynthesis:



(I)

wherein

R_1 is -alkyl-NR_3- SO_2 -X-R_4 or -alkenyl-NR_3- SO_2 –X-R_4 ;

X is a bond or –NR_5-;

R_4 is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

-O-$(alkyl)_{0-1}$-aryl;

-O-$(alkyl)_{0-1}$-substituted aryl;

-O-$(alkyl)_{0-1}$-heteroaryl;

-O-$(alkyl)_{0-1}$-substituted heteroaryl;

-O-$(alkyl)_{0-1}$-heterocyclyl;

-O-$(alkyl)_{0-1}$-substituted heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-$S(O)_{0-2}$-alkyl;

-$S(O)_{0-2}$-$(alkyl)_{0-1}$-aryl;

-$S(O)_{0-2}$-$(alkyl)_{0-1}$-substituted aryl;

-$S(O)_{0-2}$-$(alkyl)_{0-1}$-heteroaryl;

-$S(O)_{0-2}$-$(alkyl)_{0-1}$-substituted heteroaryl;

-$S(O)_{0-2}$-$(alkyl)_{0-1}$-heterocyclyl;

-$S(O)_{0-2}$-$(alkyl)_{0-1}$-substituted heterocyclyl;

-$(alkyl)_{0-1}$-NR_3R_3;

-$(alkyl)_{0-1}$-NR_3-CO-O-alkyl;

-$(alkyl)_{0-1}$-NR_3-CO-alkyl;

-$(alkyl)_{0-1}$-NR_3-CO-aryl;

-$(alkyl)_{0-1}$-NR_3-CO-substituted aryl;

-$(alkyl)_{0-1}$-NR_3-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted heteroaryl;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkyl;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and in the case of alkyl, alkenyl, or heterocyclyl, oxo;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

- alkyl-O-alkyl;

- alkyl-O- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_3)_2$;

-CO-$N(R_3)_2$;

-CO-C_{1-10} alkyl;

-CO-O-$_{C1-10}$ alkyl;

-N_3;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

-substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);

-CO-heteroaryl; and

-CO-(substituted heteroaryl);

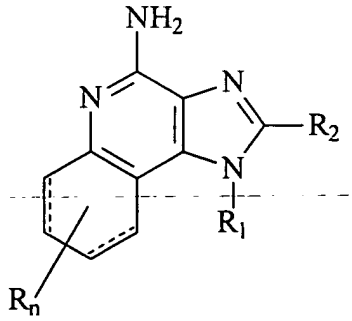
each $\mathbf{R}_3$ is independently selected from the group consisting of hydrogen and C_{1-10} alkyl;

$\mathbf{R}_5$ is selected from the group consisting of hydrogen and C_{1-10} alkyl, or $\mathbf{R}_4$ and $\mathbf{R}_5$ can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

n is 0 to 4 and each **R** present is independently selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen and trifluoromethyl,

or a pharmaceutically acceptable salt thereof that induces cytokine biosynthesis[to the animal].

31. A method of treating a neoplastic disease in an animal in need thereof comprising administering to the animal an effective amount of a compound of [claim 1]the formula (I) that induces cytokine biosynthesis:



(I)

wherein

R_1 is -alkyl-NR_3- SO_2 -X-R_4 or -alkenyl-NR_3- SO_2 –X-R_4 ;

X is a bond or –NR_5-;

R_4 is aryl, heteroaryl, heterocyclyl, alkyl or alkenyl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of:

-alkyl;

-alkenyl;

-aryl;

-heteroaryl;

-heterocyclyl;

-substituted cycloalkyl;

-substituted aryl;

-substituted heteroaryl;

-substituted heterocyclyl;

-O-alkyl;

-O-$(alkyl)_{0-1}$-aryl;

-O-$(alkyl)_{0-1}$-substituted aryl;

-O-$(alkyl)_{0-1}$-heteroaryl;

-O-$(alkyl)_{0-1}$-substituted heteroaryl;

-O-$(alkyl)_{0-1}$-heterocyclyl;

-O-$(alkyl)_{0-1}$-substituted heterocyclyl;

-COOH;

-CO-O-alkyl;

-CO-alkyl;

-$S(O)_{0-2}$ -alkyl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-aryl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-substituted aryl;

-$S(O)_{0-2}$ –$(alkyl)_{0-1}$-heteroaryl;

-$S(O)_{0-2}$-(alkyl)$_{0-1}$-substituted heteroaryl;

-$S(O)_{0-2}$-(alkyl)$_{0-1}$-heterocyclyl;

-$S(O)_{0-2}$-(alkyl)$_{0-1}$-substituted heterocyclyl;

-(alkyl)$_{0-1}$-NR_3R_3;

-(alkyl)$_{0-1}$-NR_3-CO-O-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-alkyl;

-(alkyl)$_{0-1}$-NR_3-CO-aryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted aryl;

-(alkyl)$_{0-1}$-NR_3-CO-heteroaryl;

-(alkyl)$_{0-1}$-NR_3-CO-substituted heteroaryl;

-N_3;

-halogen;

-haloalkyl;

-haloalkoxy;

-CO-haloalkyl;

-CO-haloalkoxy;

-NO_2;

-CN;

-OH;

-SH; and in the case of alkyl, alkenyl, or heterocyclyl, oxo;

R_2 is selected from the group consisting of:

-hydrogen;

-alkyl;

-alkenyl;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-alkyl-O-alkyl;

- alkyl-O- alkenyl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;

-halogen;

-$N(R_3)_2$;

-$CO\text{-}N(R_3)_2$;

-$CO\text{-}C_{1\text{-}10}$ alkyl;

-$CO\text{-}O\text{-}_{C1\text{-}10}$ alkyl;

-N_3;

-aryl;

-substituted aryl;

-heteroaryl;

-substituted heteroaryl;

-heterocyclyl;

-substituted heterocyclyl;

-CO-aryl;

-CO-(substituted aryl);

-CO-heteroaryl; and

-CO-(substituted heteroaryl);

each $\mathbf{R_3}$ is independently selected from the group consisting of hydrogen and $C_{1\text{-}10}$ alkyl;

$\mathbf{R_5}$ is selected from the group consisting of hydrogen and $C_{1\text{-}10}$ alkyl, or $\mathbf{R_4}$ and $\mathbf{R_5}$ can combine to form a 3 to 7 membered heterocyclic or substituted heterocyclic ring;

n is 0 to 4 and each **R** present is independently selected from the group consisting of $C_{1\text{-}10}$ alkyl, $C_{1\text{-}10}$ alkoxy, halogen and trifluoromethyl,

or a pharmaceutically acceptable salt thereof that induces cytokine biosynthesis[to the animal]; wherein the neoplastic disease is melanoma, hairy cell leukemia, or myelogenous leukemia.

32. A method of inducing cytokine biosynthesis in an animal according to claim 29 wherein X is a bond[comprising administering and effective amount of a compound of claim 2 to

the animal].

33. A method of treating a viral disease in an animal in need thereof according to claim 30 wherein X is a bond[comprising administering an effective amount of a compound of claim 2 to the animal].

34. A method of treating a neoplastic disease in an animal in need thereof according to claim 31 wherein X is a bond[comprising administering an effective amount of a compound of claim 2 to the animal].

35. A method of inducing cytokine biosynthesis in an animal according to claim 29 wherein X is -NR_5-[comprising administering and effective amount of a compound of claim 10 to the animal].

36. A method of treating a viral disease in an animal in need thereof according to claim 30 wherein X is -NR_5-[comprising administering an effective amount of a compound of claim 10 to the animal].

37. A method of treating a neoplastic disease in an animal in need thereof according to claim 31 wherein X is -NR_5-[comprising administering an effective amount of a compound of claim 10 to the animal].